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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 9/08	A1	(11) International Publication Number: WO 99/32086 (43) International Publication Date: 1 July 1999 (01.07.99)
(21) International Application Number: PCT/AU98/01045 (22) International Filing Date: 18 December 1998 (18.12.98) (30) Priority Data: PP 1055 19 December 1997 (19.12.97) AU (71) Applicant (for all designated States except US): SCHERING-PLOUGH ANIMAL HEALTH LIMITED [AU/AU]; 71 Epping Road, North Ryde, NSW 2113 (AU). (72) Inventor; and (75) Inventor/Applicant (for US only): SHEPHERD, Stanley [GB/AU]; 71 Epping Road, North Ryde, NSW 2113 (AU). (74) Agent: GRIFFITH HACK; G.P.O. Box 4164, Sydney, NSW 2001 (AU).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: SOLVENT/SURFACTANT INSECTICIDAL POUR-ON FORMULATION (57) Abstract A topically acceptable aqueous pour-on formulation adapted for localised external application to an animal, which format includes an effective amount of a water insoluble insect growth regulator (IGR), a suspending agent, a surfactant or mixture of surfactants, and an aqueous carrier.		

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Solvent/Surfactant Insecticidal Pour-on Formulation

Field of the Invention

The present invention relates to a pour-on formulation
5 of Insect Growth Regulator (IGR) insecticides, and a method
of treating or controlling insects and parasites on
animals. In particular, the present invention relates to a
pour-on formulation of water insoluble IGR in a non-aqueous
blend of solvent(s) and surfactant(s).

10

Background Art

In the past, animals have generally been treated for
the control of insects, and internal and external
parasites, by either dipping the whole animal in a bath
15 containing the parasitically effective agent or by
spraying the entire body surface of the animal. More
recently, it has been found that a number of
parasitically effective substances may be applied by a
localised application (so-called "pour-on" application),
20 whereby the active agent migrates so as to protect the
whole external surface of the animal. By "localised
application" it is meant that the active agent is only
applied to a minor portion of the outer surface of the
animal, generally as a line or spot on the animal's back.

25 Hitherto, the active agent has been dissolved in a
non-aqueous solvent to produce a suitable pour-on
formulation.

Existing pour-on formulations of IGRs however, have a
number of disadvantages. In particular, it has been found
30 that when in contact with water, the active ingredient may
precipitate out of the solvent formulation. Accordingly,
solvent IGR pour-on formulations are less effective if
applied to an animal which is wet, or if the animal is
exposed to heavy rain shortly after application and before
35 the treatment has dried. When pour-on formulations based
on water miscible solvents are brought into contact with

water, the active ingredient rapidly precipitates out. If an animal is treated with a non-aqueous solvent-based formulation, and is then exposed to rain, the active ingredient precipitates out of the formulation, and is deposited along the back of the animal. The insoluble active agent does not then spread around the entire animal, and is therefore less effective in treating or controlling the infestation.

10 Disclosure of the Invention

It has been found that some of the above disadvantages with prior pour-on formulations may be overcome by the use of a blend of solvent(s) and surfactant(s). The final product is an efficacious, stable, rainfast formulation of low mammalian toxicity, which is non irritant to the animal.

For example, it has been shown that IGR formulations described in the invention kill the majority of lice (>96%) within 10 weeks of application, with the remainder being killed within 15 weeks of treatment.

It has further been shown that the formulations of this invention are able to tolerate up to 10% by volume of water before the water insoluble IGR begins to slowly precipitate from the carrier solvents. This compatibility with water means that if the formulation is added to a wet animal, the active ingredient will start to spread around, but not run off, the animal. This will help to increase the efficacy of the formulation.

Likewise, if it rains shortly after the formulations of this invention are applied, the rainfall will help to spread the formulation around the animal without washing it off. This will again help to increase the efficacy of the formulation.

Additionally, the formulations also are efficacious when applied to the animal and no rain occurs for several weeks. In all these instances, it is believed that the

surfactants aid the spread of active over the surface of the animal. These beneficial effects are not obtainable at the moment with traditional solvent based formulations.

In a first aspect, the present invention provides a
5 pour-on formulation adapted for localised application to an animal, which formulation includes an effective amount of an insect growth regulator (IGR) in a blend of at least one non-aqueous solvent and at least one surfactant, wherein said solvent is chemically and physically stable, non-
10 flammable, of low mammalian toxicity and is a non-irritant to the animal.

In a second aspect, the present invention provides a method for treating or controlling insects or parasites on an animal, which method includes externally applying to an
15 animal an effective amount of a formulation including an IGR in a blend of at least one non-aqueous solvent and at least one surfactant, wherein said solvent is chemically and physically stable, non-flammable, of low mammalian toxicity and is a non-irritant to the animal.

In a third aspect, the present invention provides a method for formulating a pour-on formulation adapted for localised application to an animal, which method comprises dissolving an insect growth regulator (IGR) in a solvent by stirring at ambient temperature; adding a surfactant or
20 mixtures of surfactants and dissolving with stirring; and adding a further solvent or solvents to the mixture with stirring.

Any insoluble IGR can be used in the formulation. Suitable IGRs include diflubenzuron, triflumuron,
30 fluazuron, and methoprene. A particularly preferred IGR is diflubenzuron.

The major solvent is preferably N-methyl-2-pyrrolidone. The other solvents may include butyl digol and/or polyethylene glycol. Any other glycol ether or high
35 molecular weight polyethylene glycol could also be used.

Any anionic or nonionic surfactant could be used in this formulation. The preferred surfactants are alkyl polysaccharides, and an alkoxyated bisphenol surfactant blend.

5 Formulations intended for pour-on application (which term includes localised application by spraying) almost invariably include a colouring agent to enable the farmer or grazier to visually monitor the application of the formulation to the animal. The nature of the colouring
10 agent is unimportant, and a wide variety of suitable dyes and pigments will be known to the skilled person. The colouring agent may be soluble or insoluble in water.

 The IGR is insoluble in water. By this it is meant that the water solubility is insufficient for an effective
15 amount of the agent to be dissolved in a normal pour-on dose of the formulation.

 Active ingredients in addition to the IGR may also be incorporated in the formulation. Such actives may include actives which have an immediate effect, rather than the
20 relatively slowly acting IGR.

 Other ingredients that may be included in the formulations of the present invention are: actives which have an immediate "knock down effect" (eg synthetic pyrethroids or organophosphates); antioxidants (eg Vitamin
25 E); UV protectants (eg Oxybenzone); perfumes; and thickeners (eg polyvinyl pyrrolidone).

 Suitable ranges for the ingredients are as follows:

- | | |
|-----------------------------------|--------------|
| a) Active | 5 - 50g/L |
| b) Primary solvent | 200 - 600g/L |
| 30 c) Secondary solvent (1) | 100 - 500g/L |
| d) Secondary solvent (2) | 50 - 200g/L |
| e) Nonionic or anionic surfactant | 100 - 400g/L |

 The "normal" ratio of the above would be
a):b):c):d):e) = 1:16:12:4:8, which can also be represented
35 as active:solvents:surfactant = 1:30:10. These ratios are not expected to vary with the type of active or solvents or

surfactants. The most effective ratio is that in the "normal" formulation which has been "balanced" to optimise all of the above.

Typically, the ratio of active:pour-on
5 solvents:surfactants is about 1:30:10.

Where rainfastness and efficacy of the formulation is necessary, the following ingredients should be used: alkoxyated bisphenol surfactant blend; N-methol pyrrolidone; alkyl polysaccharide; PEG 400 and butyl digol.

10 Suitably, the ingredients are formulated as follows. Technical grade diflubenzuron is dissolved in N-methyl-2-pyrrolidone with stirring at ambient temperature in a tared manufacturing vessel. The surfactant or mixtures of
15 surfactants are added into the vessel and dissolved with stirring. Finally, the secondary solvent or solvents are added to the mixture with stirring followed by the colouring agent.

The pour-on formulation may be applied by methods known in the art. The formulation may be formulated for
20 application by a particular method, for example spraying, in which case the formulation may be presented as an aerosol using a liquid or gas propellant.

The method according to the present invention may be used to treat ticks, fleas, flies (for example, sheep
25 blowfly, buffalo fly, nuisance fly), lice (for example, cattle and sheep lice) and mites (for example, sheep mites). These species are indicative only, and the method may be used to treat a wide variety of insects and parasites on an animal. Suitably, the compositions and
30 method of this invention may be used to treat the sheep body louse which is classified as follows: Order - *Phthiraptera*, Sub Order - *Mallophaga*, Family - *Trichodectidae*, Genus - *Damalinia* (*Bovicola*, *Trichodectes*), Species - *Bovicola ovis* (Schrank).

35 The method may be used to treat or control insects and parasites on a variety of animals including sheep, cattle, deer, goats, pigs, dogs, and cats. The animal may also be a bird.

Efficacy trials are suitably carried out as follows.
40 Sheep to be studied are assessed for the number of lice at

various sites. They are then treated with the formulation of this invention at varying concentrations of active ingredient and the lice count at various sites carried out at different periods.

5

Best and other modes for carrying out the invention

Preferred embodiments will now be described by way of non-limiting examples.

10 Example 1

Table 1 Diflubenzuron Sheep Lice Pour-on		
Component	Use	g or mL/L
Diflubenzuron (pure)	Active ingredient	25.0 g
N-methyl-2-pyrrolidone (NMP)	Primary solvent	400.0mL
Alkoxylated bisphenol surfactant blend (eg Teric 163)	Non-ionic surfactant	200.0 g
Alkyl polysaccharide (eg Alkadet 20)	Non-ionic surfactant	10.0 g
Polyethylene glycol 400	Secondary solvent	100.0 g
Atcol Carmoisine	Dye	0.3 g
Diethylene glycol mono butyl ether (eg Butyl digol)	Secondary solvent	qs to 1 L

Example 2

Details of Trial

15 **Target pest**

Order -*Phthiraptera*, Sub Order -*Mallophaga*, Family - *Trichodectidae*, Genus - *Damalinia* (*Bovicola*, *Trichodectes*), Species - *Bovicola ovis* (Schrank) and Common name - Sheep body louse.

20 **Test animals**

The sheep used in this study were a uniform line of Merino wethers heavily infected with lice.

Lice assessment methodology

25 The method requires examination of twenty partings each 10cm long, along two contours on the left and right sides covering the wool growing regions of the animal. At each of the 40 recorded sites all live adult lice are counted. Site counts are summed to give a total count for

the animal.

Assessing lice populations in this manner also allows the production of a map, showing how the lice are distributed over the body of the tracer sheep.

5

Table 2 Treatment details				
Treatment	Active (mg/sheep)	Conc (g/L)	Sheep	Dose (mL)
Diflubenzuron	500	25.0	5	20
Diflubenzuron	250	12.5	5	20

Test treatments

Within 24 hours of shearing, treatments were applied as a single stripe along the backline of the sheep.

10 The dose rate applied was based on 20mL of treatment per animal which is based on all test animals being in the 30.1 - 55kg weight range.

15 The delivery apparatus for each formulation was a commercial applicator set to deliver 1 x 20mL dose to the sheep backline. The gun was calibrated using a volumetric cylinder and checked twice before and once after treatment.

20 To avoid the possibility of rain complicating the post treatment situation the sheep were kept in pens for a minimum of 48 hours. Then on the morning of the 25th day of the trial, they were placed into their paddocks.

Lice assessments were made on all sheep 2, 5, 10 and 20 weeks after treatment.

Example 3

25 **Effect of diflubenzuron in formulations at concentrations of 12.5 and 25.0 g/L on sheep lice [group arithmetic mean lice counts (standard deviations)].**

The effect of diflubenzuron in formulations of different concentrations is shown in the following table

Table 3						
Diflubenzuron Conc (g/L)	Weeks after treatment					
	0	2	5	10	15	20
25.0	126.5 (67.0)	19.4 (11.3)	2.2 (2.0)	0.2 (0.4)	0.0 (0.0)	0.0 (0.0)
12.5	121.2 (78.5)	8.6 (7.5)	0.6 (0.9)	0.4 (0.5)	0.0 (0.0)	0.0 (0.0)

Example 4

Efficacy Trial

Effect of diflubenzuron in formulations at various concentrations of 12.5 and 25.0 g/L (corrected lice count reductions) [Results of Table 3 converted to % lice reduction]

Table 4					
Diflubenzuron conc. (g/L)	% Lice reductions after:				
	2 weeks	5 weeks	10 weeks	15 weeks	20 weeks
25.0	34.8	74.1	98.1	100.0	100.0
12.5	69.9	92.7	96.1	100.0	100.0

The foregoing describes only some embodiments of the present invention and modifications obvious to those skilled in the art can be made thereto without departing from the scope of the invention.

INDUSTRIAL APPLICABILITY

It should be clear that the present invention will find wide applicablity in the agricultural and veterinary science areas.

CLAIMS

1. A pour-on formulation adapted for localised application to an animal, which formulation includes an effective amount of an insect growth regulator (IGR) in a blend of at least one non-aqueous solvent and at least one surfactant, wherein said solvent is chemically and physically stable, non-flammable, of low mammalian toxicity and is a non-irritant to the animal.

2. The formulation according to claim 1 wherein the IGR is diflubenzuron, triflumuron, fluazuron, and methoprene.

3. The formulation according to claim 2 wherein the IGR is diflubenzuron.

4. The formulation according to any one of claims 1 to 3 wherein the solvent is N-methyl-2-pyrrolidone.

5. The formulation according to any one of claims 1 to 4 wherein the surfactant is an anionic or nonionic surfactant.

6. The formulation according to claim 5 wherein the surfactant is an alkyl polysaccharide, or an alkoxyated bisphenol surfactant or blends thereof.

7. The formulation according to any one of claims 1 to 6 further comprising an actives which have an immediate effect; antioxidants; UV protectants; perfumes; thickeners; and colouring agents.

8. The formulation according to claim 7 wherein the IGR is about 5 - 50 g/L; the solvents comprise a primary solvent in an amount of about 200 - 600 g/L; a first

secondary solvent in an amount of about 100 - about 500 g/L; a second secondary solvent in an amount of about 50 - about 200 g/L; and a nonionic or anionic surfactant in an amount of about 100 - about 400 g/L.

5

9. The formulation according to claim 8 wherein the IGR is diflubenzuron.

10. A method for treating or controlling insects or parasites on an animal which includes externally applying to an animal an effective amount of a formulation including an IGR in a blend of at least one non-aqueous solvent and at least one surfactant, wherein said solvent is chemically and physically stable, non-flammable, of low mammalian toxicity and a non-irritant to the animal.

11. The method according to claim 7 wherein the IGR is diflubenzuron, triflumuron, fluazuron, or methoprene.

12. The method according to claim 8 wherein the IGR is diflubenzuron.

13. The method according to any one of claims 10 to 12 wherein the formulation is formulated as an aerosol using a liquid or gas as propellant.

14. The method according to any one of claims 10 to 14 wherein the IGR is from about 5 to about 50 g/L.

15. The method according to any one of claims 10 to 14 wherein the parasites include ticks, fleas, flies, lice and mites.

16. The method according to claim 15 wherein the flies may be sheep blowfly, buffalo fly or nuisance flies; the lice may be cattle or sheep lice; and the mites are sheep mites.

17. A method for formulating a pour-on formulation adapted for localised application to an animal, which method comprises dissolving an insect growth regulator (IGR) in a solvent by stirring at ambient temperature;
- 5 adding a surfactant or mixtures of surfactants and dissolving with stirring; and adding a further solvent or solvents to the mixture with stirring.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU 98/01045

A. CLASSIFICATION OF SUBJECT MATTERInt Cl⁶: A61K 9/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IpC : A61K 9/08

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

AU : IPC as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPAT : [DIFLUBENZURON: OR TRIFLUMURON: FLUAZURON: OR METHPRENE:] [METHYL
PYRROLIDONE] [INSECT: OR POUR:] [SURF:] [A61K/IC OR A01N/IC]CAPLUS : [DIFLUBENZURON OR TRIFLUMURON OR FLUAZURON OR METHOPRENE] AND
[METHYL PYRROLIDONE] AND [INSECT OR POUR] AND [SURFACTANT]**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5169846 A (CROOKS) 8 December 1992 whole document	1-5, 7-17
X	US 4272398 A (JAFJE) 9 June 1981 whole document	1-5, 7-17

☒ Further documents are listed in the
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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Derwent Abstract Accession No. 91-070463/10 Class C03, JP 03020201 A (DOW CHEM NIPPON KK) 29 January 1991	1-5, 7-17
A	US 5612047 (DUFFY et al) 18 March 1997 whole document	1-17

Information on patent family members

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This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report				Patent Family Member			
US	5169846	AU	64533/90	EP	427582	NZ	235647
		ZA	9008165				